AMENDMENTS TO THE DRAWINGS

Applicants enclose replacement sheets of Figures 1-24 to include sequence identifiers and color drawings. In addition, the background shading in Figures 1-2 has been removed.

Applicants have identified the replacement drawings as a "Replacement Sheets."

REMARKS

Applicants wish to thank Examiner Lin for the helpful interview with the undersigned on November 8, 2007. During the interview, various issues and options were discussed, including the rejections under 35 U.S.C. § 112 and possible amendments to overcome the rejections.

Claims 1-2, 4, 6-7, 13, 23-24, 26-27, 30, 33-34, 42, 44-45, and 47 have been amended without any intention of disclaiming equivalents thereof. Claim 5 has been cancelled without prejudice to its subsequent reintroduction into this application or its introduction into a related application. Upon entry of this paper, claims 1-4, 6-8, 13, 19-21, 23-24, 26-28, 30-34, 42, and 44-47 will be pending and under consideration.

Claims 1, 30, and 42 have been amended to recite an RNA spanning a splice junction. Support for this amendment appears throughout the application as filed, for example, on page 98, lines 27-28 of the application as filed. Claim 1, step (2) has been amended to recite generating a plurality of capture agents. Support for this amendment appears throughout the application as filed, for example, from page 42, line 4, to page 56, line 9 of the application as filed. Claim 1, step (4) and claim 42, step (3) have been amended to recite detection using a secondary capture agents specific for sites separate from the PETs or specific for available sites on the respective captured polypeptides, respectively. Support for this amendment appears throughout the application as filed, for example, from page 42, line 24 to page 43, line 7 of the application as filed. In addition, claims 1-2, 4, 6-7, 13, 23-24, 26-27, 33-34, 42, 44-45, and 47 have been amended with regard to antecedent basis, usage of singular and plural nouns, and/or for grammar.

Applicants have amended the specification to indicate that the patent or application file contains color drawings. In addition, Applicants have amended paragraphs and Tables in the specification and have amended the Figures to include sequence identifiers in accordance with 37 C.F.R. §1.821. Figures 1-2 also have been amended to remove the background shading. Applicants believe that the aforementioned amendments to the claims, specification, and Figures introduce no new matter.

Response to Formal Objections

According to Sections 2 and 3 of the outstanding Office Action, the Office has required that sequence identifiers be included in the specification and Figures. In addition, the Office has required replacement sheets for Figures 1 and 2. Applicants have amended the specification and Figures to address each of these issues and respectfully request that these objections be reconsidered and withdrawn.

According to Section 4 of the outstanding Office Action, the Office has indicated that color drawings were submitted to the Office on February 5, 2004, and has required a Petition to Accept Color Drawings, the appropriate fee, additional sets of color drawings, and amendment of the specification to indicate that the patent or application file contains color drawings. Applicants have filed herewith the requisite documents and have amended the specification to address this issue. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

Rejections under 35 USC § 112, First Paragraph

According to Section 5 of the outstanding Office Action, claims 1-8, 13, 19-21, 23, 24, 26-28, 42, and 44-47 have been rejected under 35 U.S.C. § 112, First Paragraph. Applicants understand that this rejection is directed to step (4) in each of claims 1 and 42, in view of Applicants' arguments in Applicants' Amendment and Response filed May 17, 2007. Without acquiescing to this rejection but in order to promote prosecution, Applicants have amended step (4) in each of claims 1 and 42 (now step (3) in claim 42) to recite that the secondary capture agents are specific for sites on the polypeptide analytes apart from the sites bound by the first capture agents. Accordingly, in view of these amendments, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph

According to Section 7 of the outstanding Office Action, claims 1-8, 13, 19-21, 23, 24,

26-28, 30-34, 42, and 44-47 have been rejected under 35 U.S.C. § 112, Second Paragraph. Specifically, the Office Action has alleged that certain claims are indefinite with respect to antecedent basis and usage of singular and plural nouns. Applicants understand that this rejection is directed to each of claims 1, 2, 4, 5, 6 and 47, 7 and 13, 23 and 24, 27, 34, 42, and 45 for the reasons indicated at pages 7-9 of the Office Action. Without acquiescing to this rejection but in order to promote prosecution, Applicants have canceled claim 5 and amended each of these remaining claims in accordance with the discussion between Examiner Lin and the undersigned on November 8, 2007. Applicants respectfully submit that each of these pending claims, as amended, is definite and therefore respectfully request reconsideration and withdrawal of this rejection.

Rejections Under 35 U.S.C. § 103(a)

According to Sections 8-9 of the outstanding Office Action, claims 1, 3-5, 19, 24, 26, 28, 30-34, 42, 44, and 46 have been rejected under 35 U.S.C. § 103(a) as being obvious over Dours-Zimmermann *et al.* (1994) J. Biol. Chem. 269(52): 32992-98 ("Dours-Zimmermann") in view of Jemmerson *et al.* (1987) Proc. Natl. Acad. Sci. USA 84: 9180-84 ("Jemmerson") in view of Arenkov et al. (2000) Anal. Biochem. 278: 123-31 ("Arenkov"). In addition, according to Sections 8 and10 of the outstanding Office Action, claims 2, 6-8, 13, 20-23, 26-27, 45, and 47 have been rejected under 35 U.S.C. § 103(a) as being obvious over Dours-Zimmermann in view of Jemmerson in view of Arenkov, further in view of United States Patent No. 6,897,073 by Wagner *et al.* ("Wagner"). Applicants respectfully request reconsideration and withdrawal of these rejections in view of the present amendments and following remarks.

The claimed subject matter of the present invention enables the measurement of proteins in a sample that include one or more proteins that are expression products of an alternative splicing form of DNA. Sample proteins are fragmented using a predetermined protocol to generate peptide epitope tags (PETs) that are unambiguously indicative of the target proteins in the sample. In Applicants' Amendment and Response filed May 17, 2007, Applicants amended the independent claims of the present invention to require that at least one of the target protein PETs or recognition sequences comprise an amino acid sequence encoded by RNA comprising a

splice junction. Moreover, for the target proteins with PETs or recognition sequences comprising an amino acid sequence encoded by an RNA comprising a splice junction, detection is facilitated by identification of the amino acid sequence corresponding to the splice junction.

As Applicants explained previously, this claimed invention is particularly useful for identifying in a sample each of two or more splice variant proteins having sequences encoded by RNA from the same exons. For example, in a sample comprising protein A_1 comprising the product of the DNA sequence exon A - intron - exon B; protein A_2 comprises the product of the DNA sequence exon A - intron - exon C; and protein A_3 comprises the product of the DNA sequence exon B - intron - exon C, the method of the present invention allows for the unambiguous identification of each protein by detecting, for example, the splice junction between the exons A-B, A-C, and B-C. By comparison, detection of exon A, or exon B, or exon C alone would not allow for the unambiguous identification of any of proteins A_1, A_2, or A_3. Applicants respectfully submitted in the previous Amendment and Response that none of the cited references, alone or in combination, describe at least this feature of the present invention. The same is true for the references cited in the outstanding Office Action.

The outstanding Office Action alleges that Applicants' limitation of comprising an amino acid sequence encoded by an RNA comprising a splice junction does not require necessarily comprising an amino acid sequence encoded by an RNA at a splice junction. Office Action, page 11, first full paragraph. While respectfully disagreeing with the Office's interpretation that RNA comprising a splice junction does not necessarily include RNA at a splice junction, Applicants currently have amended the independent claims of the present invention to address the Office's allegation.

Specifically, independent claims 1 and 42 have been amended to require, in part, generating a polypeptide analyte comprising - , a capture agent that specifically binds to - , and detecting the polypeptide analyte comprising - a PET or recognition sequence comprising an amino acid sequence encoded by an RNA spanning a splice junction. Similarly, independent claim 30 has been amended to require, in part, an array of capture agents specifically binding to recognition sequences comprising peptide epitope tags (PETs), at least one of said PETs comprising an amino acid sequence encoded by an RNA spanning a splice junction. Applicants

respectfully submit again, in this Amendment and Response, that none of the cited references, alone or in combination, describe at least this feature of the present invention.

For example, the Office's primary reference, Dours-Zimmerman, does NOT describe or suggest using or raising capture agents against amino acid sequences encoded by RNA spanning a splice junction, as required by Applicants' claims. Rather, Dours-Zimmermann describes a method for identifying two different splice forms (V_1 and V_0) for the protein, versican, using antibodies raised against amino acid sequences encoded by RNA comprising two splice domains, GAG-alpha and GAG-beta, not splice junctions. Page 32933, left column, fourth full paragraph; page 32995, paragraph bridging left and right columns; page 32996, Figure 4; and page 32998, Figure 7. Specifically, Dours-Zimmerman's splice form V_0 comprises both the GAG-alpha and GAG-beta splice domains and therefore can be identified by both anti-GAG-alpha and anti-GAG-beta antibodies, while the splice form V_1 comprises the GAG-beta splice domain, and not the GAG-alpha splice domain, and therefore can be identified by the anti-GAG-beta antibody only. Page 432996, Figure 4; page 32998, Figure 7. Accordingly, the Dours-Zimmerman method fails to teach or suggest making or using a capture agent against an amino acid sequence encoded by RNA spanning a splice junction, as required by Applicants' claims.

The Office's secondary references, Jemmerson, Arenkov, and Wagner, are silent as to amino acid sequences encoded by an RNA spanning a splice junction. Accordingly, since none of the cited references teach or suggest, alone or in combination, at least this element of Applicants' independent claims 1, 30, and 42, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 30, and 42, and all claims depending therefrom.

CONCLUSION

Applicants invite the Examiner to contact the undersigned Attorney to discuss any remaining issues with this application. Applicants believe that the claims are in condition for allowance. Early favorable action is respectfully solicited.

Respectfully submitted,

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